Peripheral arterial disease

Isoform-specific antibody unlocks new treatment pathway

Atherosclerosis is a common condition in which the accumulation of fibrofatty deposits or plaques inside the arteries can cause blockages that reduce blood flow to the limbs. In response, the body normally forms new, smaller blood vessels to bypass the blockage and maintain circulation to affected tissues, a process known as collateralisation. However, in peripheral arterial disease (PAD), collateralisation is inhibited and without sufficient blood flow to deliver essential oxygen and nutrients to the limbs, tissues progressively deteriorate, a condition termed ischaemia, resulting in pain and other debilitating symptoms. PAD is known to affect around 200 million people globally. In severe cases, it can progress to chronic limb threatening ischaemia (CLTI), where blood flow becomes so limited, patients are faced with amputation of lower limbs.

Type 2 diabetes (T2D) is considered the biggest risk factor for PAD and is present in 25% of cases, with an estimated 11% progressing to CLTI. Other risk factors include high blood pressure, high cholesterol and BMI, as well as lifestyle factors such as smoking and an unhealthy diet. The only drug treatments available focus on managing these risk factors or controlling symptoms, rather than addressing the cause of ischaemia. Surgery is sometimes an option for large arterial blockages, and may involve vessel bypass, stenting (limited to above-the-knee procedures), and endovascular angioplasty. Unfortunately, these are often only partially successful in restoring blood flow, can result in high rates of restenosis (re-narrowing of arteries) and are not viable for all patients, especially those with comorbidities like diabetes, who often experience poor outcomes or are not suitable candidates for surgical interventions.

IsomAb, a UK based biotechnology company, is developing isoform specific antibodies to treat ischaemic diseases for which there are limited or no treatment options; its first development candidate, ISM-001, will be trialled in patients with T2D and CLTI. The antibody specifically targets and inhibits the VEGF-A_{165}b isoform of vascular endothelial growth factor-A (VEGF-A), which is a key protein involved in the regulation of angiogenesis—the process of forming new blood vessels—particularly in ischaemic conditions. Based on 20 years of discovery research by IsomAb's two founders, the evidence strongly supports that reducing levels of VEGF-A_{165}b can promote new blood vessel formation, helping to restore blood flow to tissues affected by ischaemic diseases.

This article explains how the founders discovered this important isoform, what isoform specific antibodies are, and why they are beneficial, and how IsomAb is developing ISM-001 to tackle ischaemic diseases resulting from PAD.

The discovery of VEGF-A_{165}b

Vascular endothelial growth factor-A (VEGF-A) is a protein that plays a crucial role in regulating blood vessel growth (angiogenesis) and is a member of the larger VEGF superfamily. It can exist in multiple isoforms, which are different versions of the same protein, arising from the process of alternative splicing of mRNA. The proteins with slightly different sequences can have different biological functions. For example, VEGF-A isoforms can have different effects on angiogenesis - some may be associated with disease progression, while others maintain essential physiological roles.

VEGF-A_{165}a is a well studied pro-angiogenic isoform of VEGF-A that drives the growth of new blood vessels by binding to VEGF receptors on the surface of endothelial cells; this stimulates the proliferation and migration of these cells.

IsomAb founders and world-renowned experts in VEGF biology, Professors David Bates and Steve Harper, originally both working at the University of Bristol and subsequently Professor Bates at the University of Nottingham, both in the UK, discovered a previously unknown splice variant of VEGF-A, which is named VEGF-A_{165}b. They uncovered this new isoform while researching how angiogenesis is regulated, particularly in the kidney's glomeruli. They found that VEGF-A_{165}b was present in normal human kidney tissue, but reduced in renal carcinoma, a type of kidney cancer where abnormal blood vessel growth supports tumour development. Further investigation showed that VEGF-A_{165}b had anti-angiogenic properties, meaning it inhibits blood vessel growth.

Over the past decade, many independent studies have confirmed their findings. Researchers have identified that the normal angiogenesis process is dependent on the balance between the two isoforms, VEGF-A_{165}a and VEGF-A_{165}b. They found that VEGF-A_{165}b is up-regulated in PAD patients with diabetes and obesity, with higher levels closely linked to increased disease severity. When VEGF-A_{165}b levels are high, the normal angiogenic signaling process that promotes blood vessel growth is inhibited, even in the presence of VEGF-A_{165}a. Therefore, blocking the activity of VEGF-A_{165}b through targeted therapies could remove this 'brake,' allowing VEGF-A_{165}a to promote angiogenesis and improve blood supply in ischaemic tissues.

A new approach to treating PAD

IsomAb exclusively licensed the research from the University of Nottingham and has developed ISM-001; a humanised IgG1, neutralising antibody which specifically targets VEGF-A_{165}b. Many therapeutics target areas of a protein that are found in all its isoforms, which can lead to reduced clinical effect and undesirable side effects. Isoform-specific antibodies however allow for precise targeting, selectively inhibiting or modulating the disease-related isoform without affecting others. This specificity reduces off-target effects and improves therapeutic outcomes.

Collaboration with Pfizer

On 15 October, IsomAb announced the start of a strategic collaboration with a unit of Pfizer Inc to develop its experimental drug for peripheral arterial disease. Pfizer Ignite, an incubator, supports biotech companies that fit within the parent company's strategic focus and show potential to be breakthrough therapies. The collaboration will enable the preclinical development of IsomAb's candidate drug ISM-001 which is designed to neutralise an isoform that acts as a brake on the development of new blood vessels leading to chronic limb threatening ischaemia. The preclinical studies are expected to lead to first-in-human clinical trials.

ISM-001 works by specifically binding to VEGF-A_{165}b, neutralising its inhibitory effect on angiogenesis. This enables the body to develop a new network of blood vessels around blocked or damaged arteries, increasing blood flow, oxygen delivery, and tissue repair in ischaemic areas. In contrast to current treatments, ISM-001 addresses a pathway in the pathophysiology of PAD, rather than managing the symptoms or focusing on general risk factors. This could potentially reduce the reliance on surgical interventions and lower the rates of limb amputations and mortality, which currently stand at 15-20% and 15-40% respectively, within one year of diagnosis.

IsomAb's development plan initially focuses on using ISM-001 to treat patients suffering T2D and/or obesity with CLTI. *In vivo* pharmacology studies have shown ISM-001 to be effective, including models where previous therapies have failed, highlighting its promise as a breakthrough treatment for PAD and related ischaemic conditions.

In one study, mice were induced with type 2 diabetes through a high fat/high sucrose diet and hind limbs were surgically ligated to simulate PAD. The study assessed blood flow restoration in mice treated with ISM-001, with a chimeric (mouse-human) antibody, and with a non-specific human IgG control to evaluate ISM-001's efficacy. The results showed that ISM-001 restored blood flow to pre-operative levels within 28 days.

These findings were further validated in a second study involving diabetic rats that also underwent surgical ligation of their limbs to mimic ischaemic conditions. In this study, the rats treated with ISM-001 were compared to those receiving a control antibody. The results demonstrated that ISM-001 significantly improved blood flow and promoted revascularisation in the treatment group.

A brighter future for patients with ischaemic disease

ISM-001 has a unique mechanism of action and is the first therapy to target the VEGF-A_{165}b pathway. Its preclinical success in promoting angiogenesis and restoring blood flow shows its potential as a promising novel therapy for the treatment of PAD and CLTI, offering new hope to millions of patients who currently have few options and face the risk of disease progression or amputation.

IsomAb is progressing ISM-001 through pre-clinical studies prior to first-in-human (FIH) trials, marking an exciting step toward bringing ISM-001 to patients. FIH trials will involve both healthy volunteers and patients with PAD and CLTI. The focus of the Phase 1 studies will be on evaluating the safety, tolerability, and pharmacokinetics of ISM-001, as well as its ability to reduce VEGF-A_{165}b levels and promote blood flow restoration in ischaemic tissues.

Looking ahead, ISM-001 could be expanded beyond CLTI to treat other ischaemic conditions in which blood flow is restricted and there are few treatments, such as coronary artery disease, stroke, systemic sclerosis and ischaemic kidney disease. If successful, ISM-001 would address a huge unmet need and significantly improve outcomes for patients.

References

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